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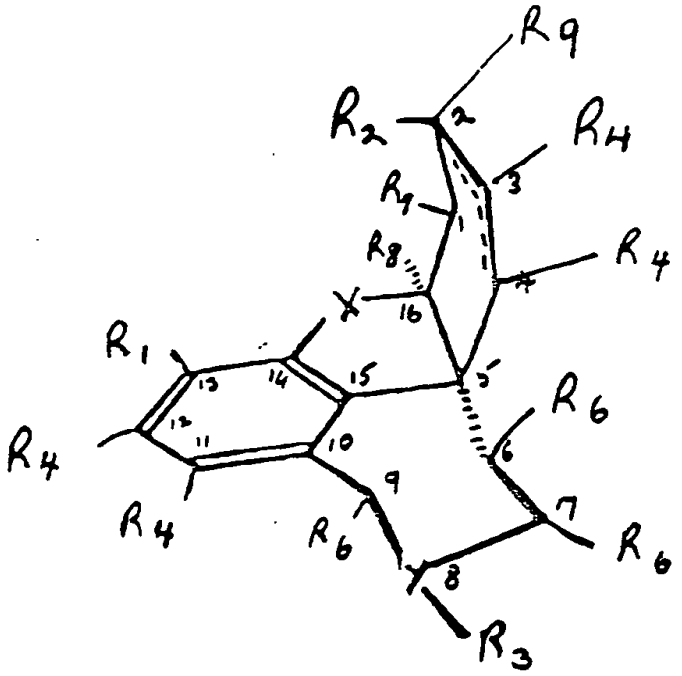

(I)

(57) Abstract

Compounds of formula (I) are of use in treating Alzheimer's disease.

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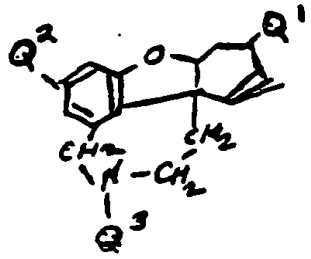
Compounds for the Treatment of Alzheimer's Disease

The present invention is directed to galanthamine-analogues and their preparation and use for treatment of Alzheimer's disease.

United States Patent No. 4,663,318 issued on May 5, 1987 describes the use of galanthamine for the treatment of Alzheimer's disease and related dementias.

Published European Patent Application 236684 describes the use of galanthamine and certain analogues for the treatment of Alzheimer's disease and related dementias, such analogues have the formula:

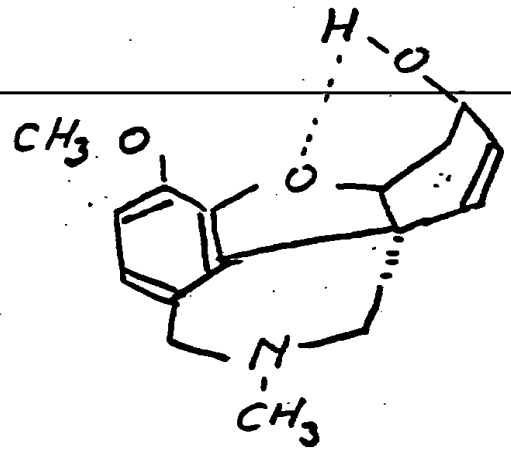


wherein Q^1 is methoxy, ethoxy, lower alkanoyloxy or oxy,

Q^2 is hydrogen, methoxy, ethoxy or lower alkanoyloxy and Q^3 is straight or branched chain alkyl group, or cycloalkyl alkyl group, allyl or substituted lower alkyl phenyl and analogues thereof wherein hydrogen atoms are replaced by chloro or fluoro atoms.

Without wishing to be bound by any theory, we now believe that the activity of galanthamine probably stems from the fact that a hydrogen bond between the hydroxyl group and the oxygen of the furan ring helps to stabilize its

cyclohexene ring in a boat rather than a chair configuration:

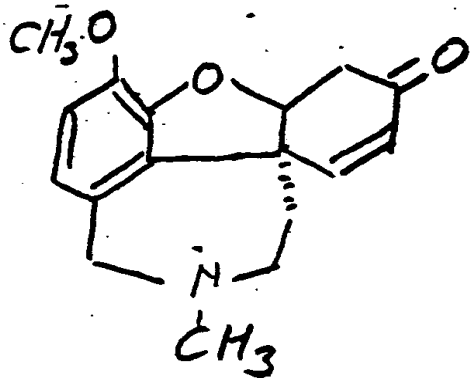


The literature shows the epigalanthamine wherein the hydroxy group is in the equatorial position so that hydrogen bond stabilization of structure is not possible has an anti-cholinesterase activity of only 10% of galanthamine. (Chemical Abstracts Vol. 77 Abstract 109461s)

A number of galanthamine analogs occur naturally or have been obtained from natural products including the following compounds described in the text book The Alkaloids (edited by published by , the Edition):

Narwedine:

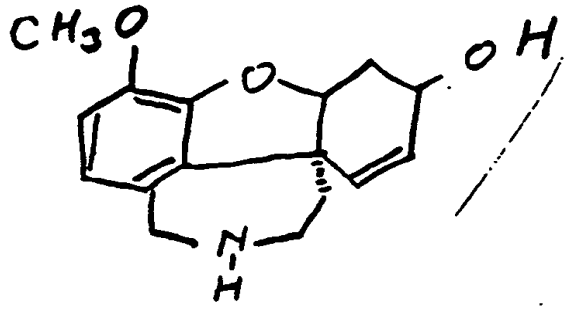
(also referred to sometimes as galanthaminone)



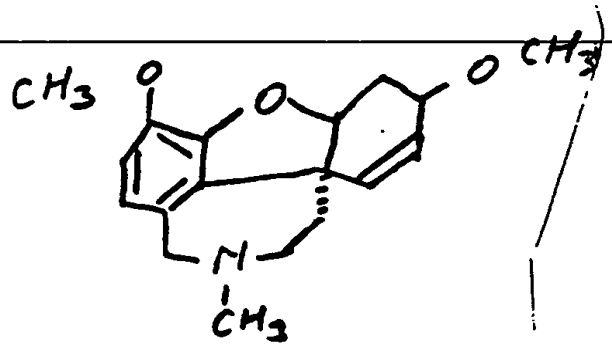
Narwedine has been reported to have weak anticurare activity at 3 mg/kg (Chemical Abstracts Vol. 78 Abstract 131941r) and to have ch linergic effects on respiration and

heart activity 50-80% lower than galanthamine (Chemical Abstracts Vol. 80 Abstract 103864r), Schmidt et al in Acta Biol Med Ger (7) 402-410 (1961) report that the anticholinesterase activity of Narwedene is less than 1% of that of galanthamine.

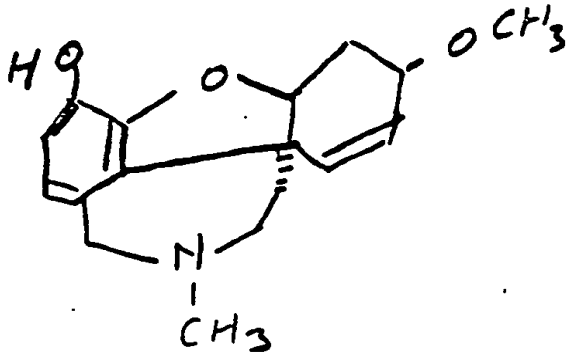
(-) N-demethyl galanthamine:



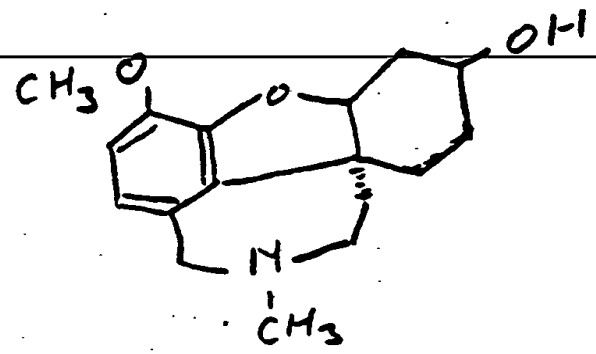
Galanthamine O methyl ether:



Childanthine:

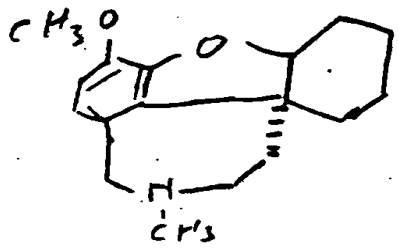


Lycoramine:

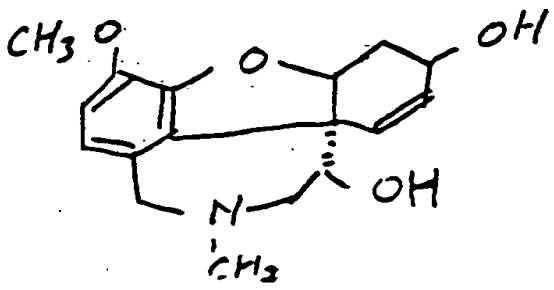


It has been reported that the concentration of lycoramine required to stimulate EEG - recorded activity is about five times that required for galanthamine (Chemical Abstracts Vol. 62 Abstract 15306e).

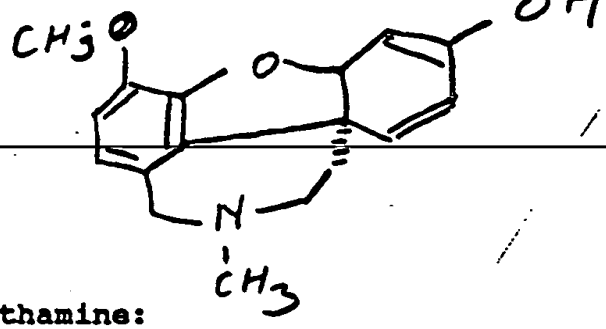
Deoxy lycoramine



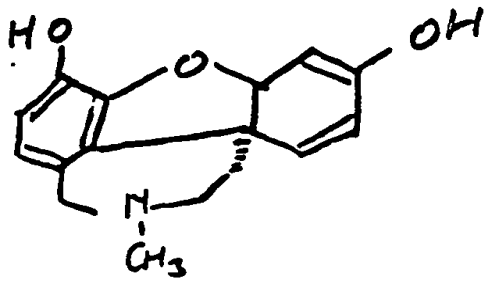
Habranthine:



Anhydrogalanthamine:

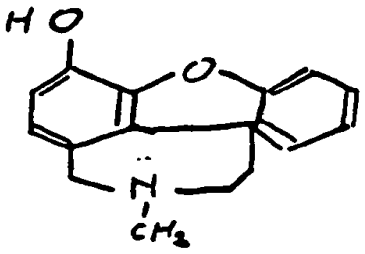


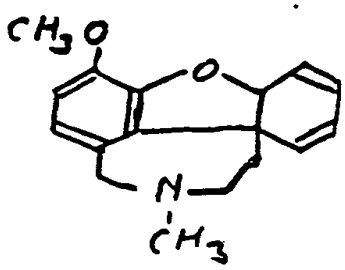
Anhydro-O-demethylgalanthamine:

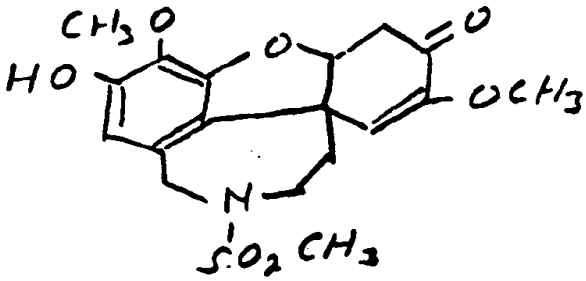


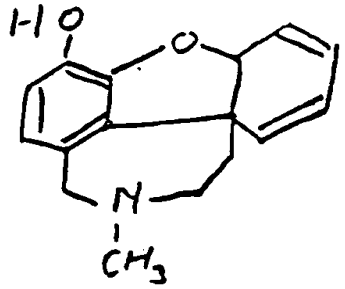
and N-mesityl and N-benzyl derivatives of galanthamine.

Reference is also made to compounds of the formulae:



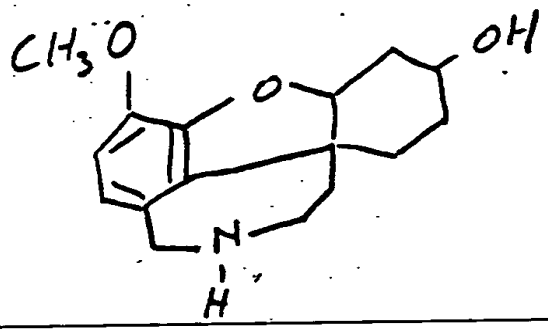




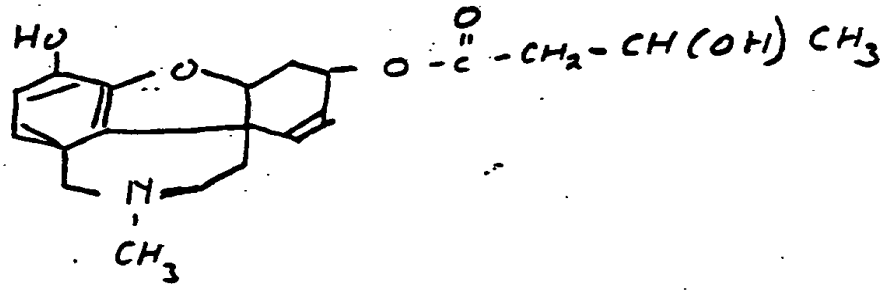


The latter compound has been reported to have activity similar to that of galanthamine (J Chem Soc (C) p 1043 (1971)

An earlier edition of this book had also referred to (+) N-demethyl dihydrogalanthamine of the formula:



N-demethyl dihydrogalanthamine is described by Kametani et al in J. Heterocyclic Chemistry 1973 10(1) 35-7. The same paper also refers to galanthamine O, N diacetate Leucotamine

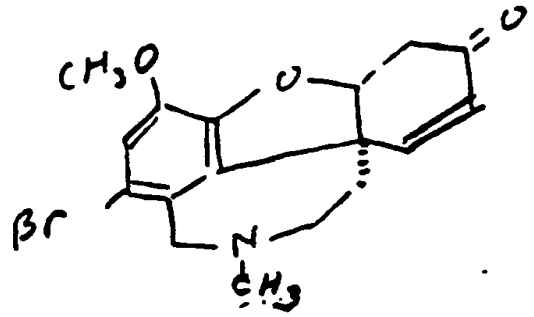


and its O-methyl and O-methyl acetic acid ester are described by Kobayashi et al in Chem. Pharm. Bull. 33 p 5258 (1985).

O-Demethyldihydrogalanthamine (also known as O-demethyl lycoramine) and O-demethyl galanthamine (sanguinine)

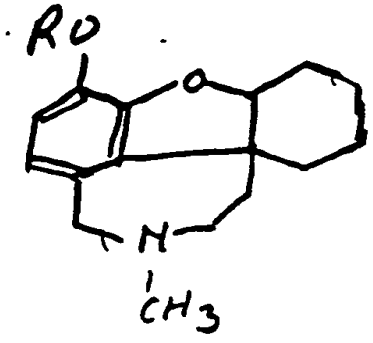
are described by Kobayashi et al in Chem. Pharm. Bull. 28 3433-3436 (1980).

A bromo-narwedine of the formula:



is described as an intermediate in the synthesis of galanthamine by Kametani et al in Chem. Comm. 1969 p. 425 and J. Chem. Soc. (C) (1969) 2602.

Chemical Abstracts 61 14727g Chem Pharm Bull 12 1012-20 (1964) describes the production of compounds of the formula:

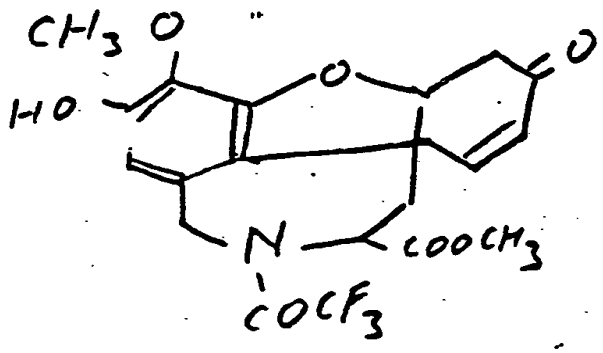


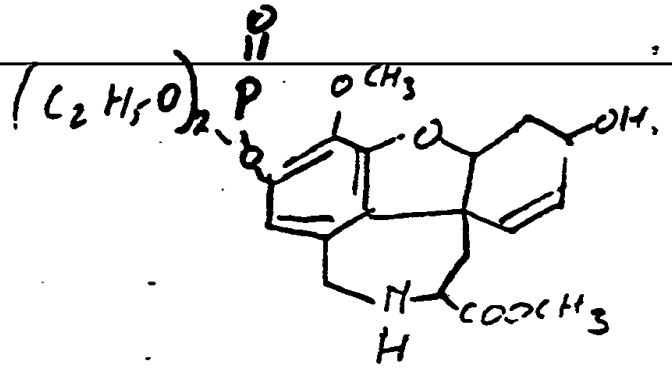
wherein R may be hydrogen, methyl or ethyl.

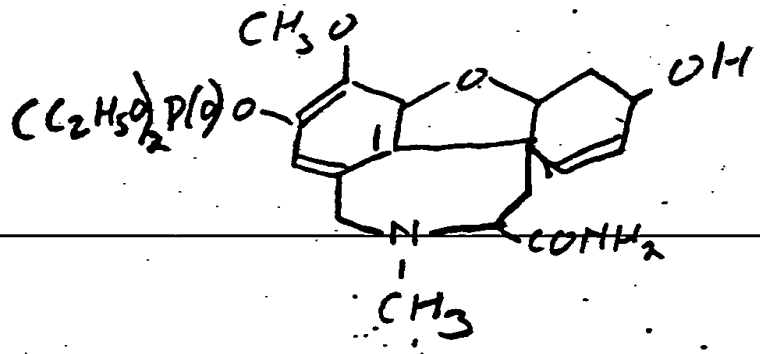
Chemical Abstracts 81 638193 describes n.m.r. studies on dihydrogalanthamine and its acetic acid esters.

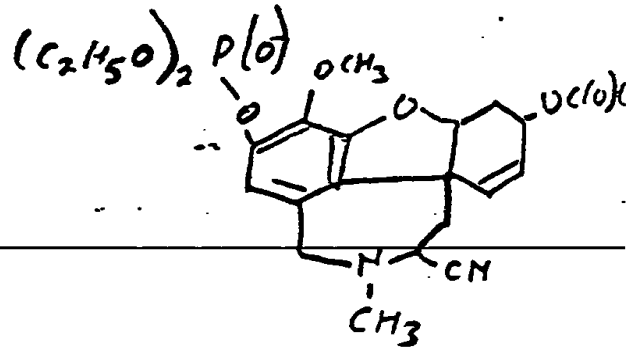
Shimizu et al in Heterocycles 1977 8 pages 277-82 (abstracted in Chemical Abstracts 88 136821t) describe certain

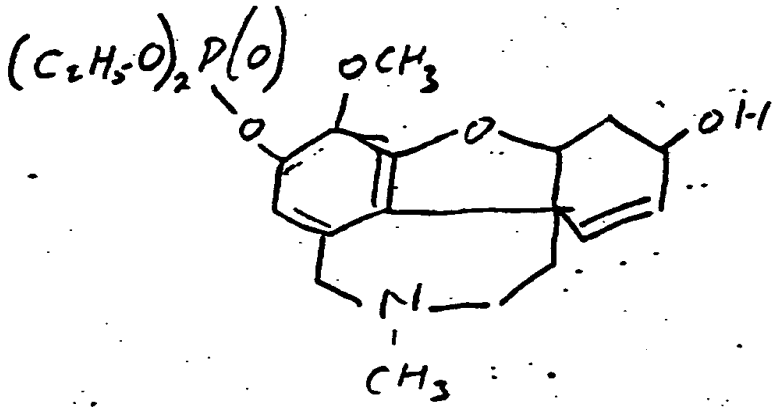
narwedine derivatives used as intermediates having the following formulae:

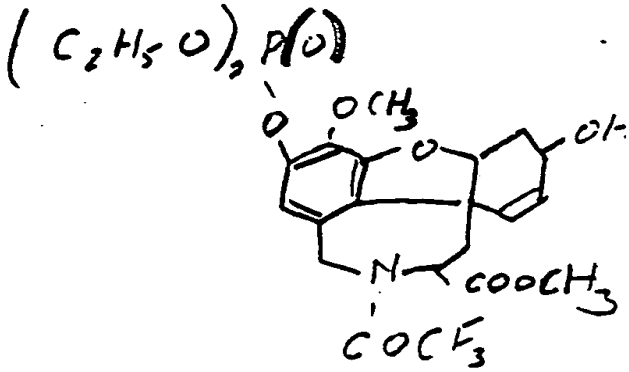


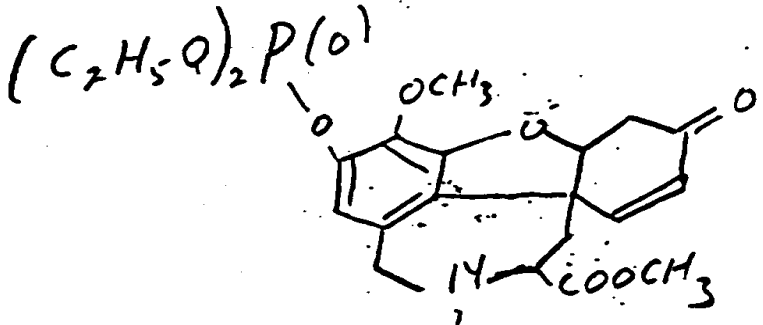


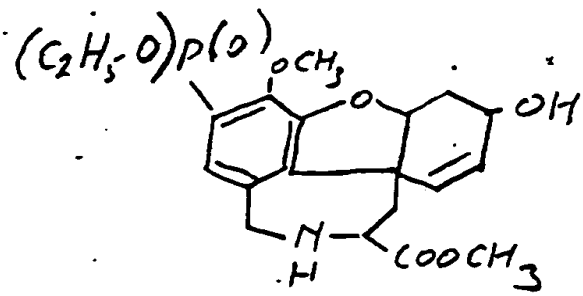












Irwin and Smith in Arch Int. Pharmacodyn 1960 CXXLII pages 3-14 et seq. described the cholinesterase activity of galanthamine and some of its analogues including lycoramine acetate methiodide, neopin methiodide (both of which were ineffective) and deoxydemethyl lycoramine methiodide (which demonstrated good activity) and deoxylycoramine (which exhibited some activity). It was hypothesized that the presence of a free hydroxy group in the cyclohexane ring conferred activity on the molecule since the acetylation of this group led to a drop in activity.

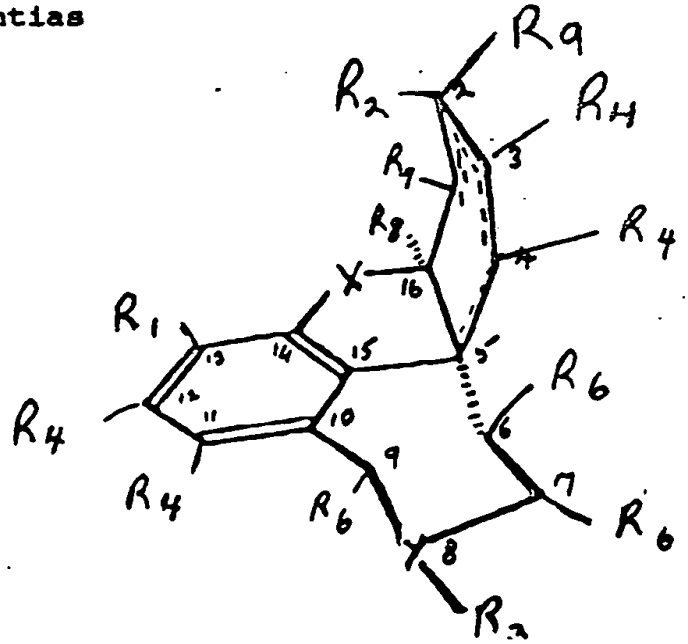
In J Pharmacol & Exptl Therap Irwin, Smith and Hein expanded on the work just described and reported that replacement of the hydroxyl group of deoxydemethyl lycoramine methiodide by a carbamate group resulted in useful pharmacological activity.

Subsequently, In Irwin and Hine J Pharmacol & Exptl Therap (196) Vol. 136 p 20) described the activity of a number of carbamates including deoxydemethyl lycoramine carbamate on cholinesterase activity in rat brain.

Subsequently, Somers et al in Neurology 13 p. 543 reported that some of Irwin's compounds were useful in treating myasthenia gravis.

Detailed Description of the Invention

The present invention relates to the use of compounds of the formula I to treat Alzheimer's disease and related dementias



wherein the broken line represents an optionally present double bond in one of the two portions shown, R_1 and R_2 are each selected independently from the group consisting of hydrogen, hydroxyl, amino or alkylamino, cyano, sulfhydryl, alkoxy preferably of 1-6 carbon atoms, alkylthio, aryloxy, arylthio, R_5-substituted aryloxy, R_5-substituted arylthio, aralkoxy, aralkylthio, R_5-substituted aralkoxy, R_5-substituted aralkylthio, aryloxymethyl, R_5-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_5-substituted benzoyloxy, aryloxy carbonyl and R_5-substituted aryloxy carbonyl, R_1 may also by alkyl of up to 14 carbon atoms, a mono or dialkyl or aryl carbamyl group or hydroxy methyl, R_2 may also be carboxymethyl provided that at least one of R_1 and R_2 is hydroxy, amino or alkylamino unless R_7 or R_8 is hydroxymethyl,

R_3 is hydrogen, straight or branched chain alkyl, preferably of 1-6 carbon atoms, cycloalkyl methyl, alkylphenyl, R_5-substituted alkylphenyl, heterocyclyl such as α- or ß-furyl, α- or ß-thienyl or thenyl, pyridyl, pyrazinyl or pyrimidyl groups, alkyl heterocyclyl and R'-substituted heterocyclyl, where R' is alkyl or alkoxy

each R_4 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, aryl, aralkyl, alkoxy, thioalkoxy, aryloxy, thioaryloxy, alkarloxy, thioalkaryloxy, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo iodo and trifluoromethyl, and R_5 is selected from the same groups as R_4,

R_6 is hydrogen, halo, trifluoromethyl or alkyl of 1 to 4 carbon atoms,

R_7 is selected from the same groups as R_4 or may be hydroxy alkyl of 1-2 carbon atoms,

R_8 is hydrogen or hydroxymethyl,

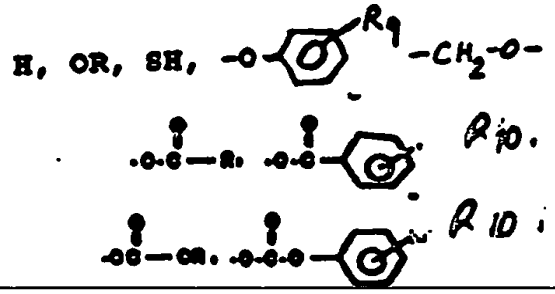
R_9 is hydrogen alkyl of 1 to 6 carbon atoms, phenyl or benzyl, or when R_2 is hydroxyl R_9 may be a moiety of formula I wherein R_9 is hydrogen and R_2 is a linking bond; or R_2 and R_9 may jointly form a semi carbazone,

X is oxygen or NR_5,

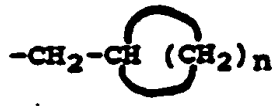
Y is nitrogen or phosphorus, preferably nitrogen, and methylenedioxy derivatives thereof with the proviso that when X is O, R_3 is not methyl when R_1 is methoxy, R_2 is hydroxy, and all R_4 are hydrogen or a pharmaceutically-acceptable acid addition salt thereof. When there is no unsaturation in the 1,2 carbon bond, R^2 is preferably oriented axially to the cyclohexane ring.

Preferably the aryl groups are phenyl groups, the aryloxy groups are phenoxy groups, the aralkyl groups are benzyl groups and the aralkyloxy groups are benzyloxy groups.

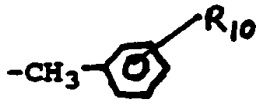
Preferred compounds include those wherein R^1 and R^2 are each selected from



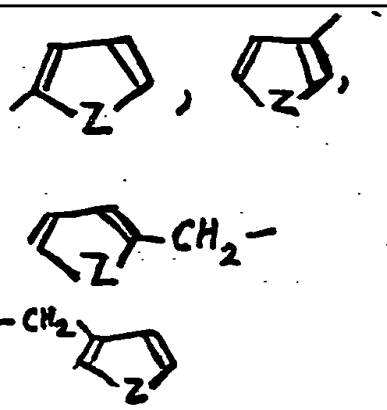
wherein R is alkyl 1-6 carbon atoms or phenyl or R^5-substituted phenyl or benzyl or R^5-substituted benzyl, wherein R_{10} is hydrogen, alkyl or alkoxy, R_3 is -H, or branched on linear alkyl or



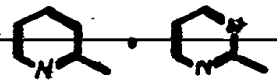
wherein n is 3, 4 or 5



wherein R_{10} is as defined above



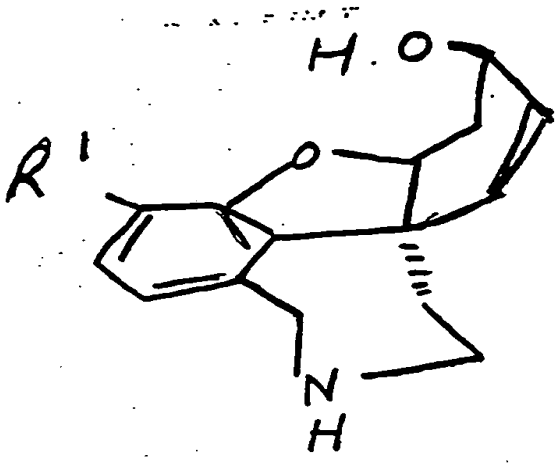
where Z is O, S, or NH

or 

X is oxygen and Y is nitrogen.

When used herein the term "lower alkyl" means alkyl of 1-6 carbon atoms, preferably 1-4 carbon atoms, most commonly methyl or ethyl.

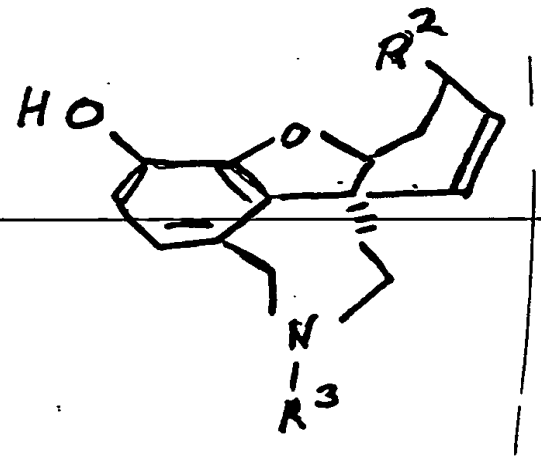
One class of compounds according to the present invention are those of the formula:



wherein R^1 is as defined abov , preferably hydroxy, lower alkoxy, aryloxy, R^5 substituent aryloxy, benzyloxy or R^5 substituted benzyloxy, amino, alkyl amino or an alkyl or aryl carbamyl group.

For example, such compounds include O-demethyl, N-demethyl galanthamine; O-ethyl, O-demethyl, N-demethyl galanthamine; O-phenyl, O-demethyl, N-demethyl galanthamine; and O-benzyl, O-demethyl galanthamine. Useful carbamates may include phenyl carbamyl O-demethyl, N-demthyl galanthamine; mono ∝- naphthyl carbamyl O-demthyl N-demethyl galanthamine and dimethyl carbamyl O-demethyl, N-demethyl galanthamine.

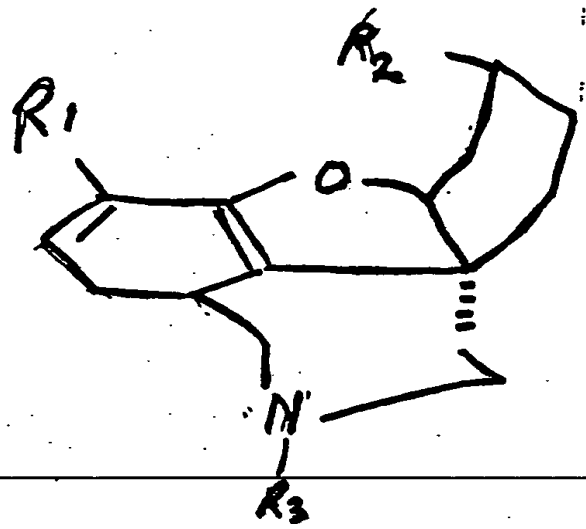
A second class are those of the formula:



wherein R^2 is hydroxy, lower alkoxy, arloxy, R^5 substituted arloxy benzyloxy or R^5 substituted benzyloxy or an alkyl or aryl carbamyl group and R^3 is hydrogen or alkyl of 1-6 carbon atoms such as methyl or ethyl, methyl cyclopropyl or benzyl or R^5-substituted benzyl. Such compounds include O-demethyl galanthamine; O-demethyl galanthamine; O-methyl ether; O-demethyl galanthamine; O-ethyl ether; O-demethyl galanthamine, O-benzyl ether; O-demethyl galanthamine, phenyl and O-demethyl N-demethyl galanthamine, ∝-naphthyl carbamates; O-demethyl galanthamine dimethyl carbamate and O-dimethyl galanthamine

diethyl carbamate wherein the carbamyl group is bonded to the oxygen of the cyclohexene ring, and the corresponding N-demethyl and N-demethyl N-ethyl and N-demethyl N-cyclopropyl methyl and N-demethyl N-benzyl compounds.

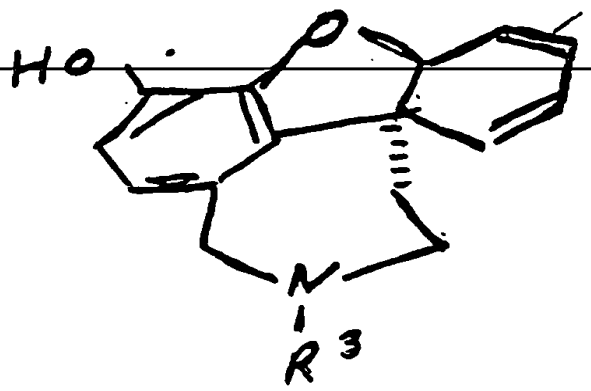
A third class of compounds comprises those of the formula:



wherein R^1, R^2 and R^3 are as defined above, R^1 typically being hydroxy, lower alkoxy, benzyloxy or R^5 substituted benzyloxy, amino alkylamino or alkyl or aryl carbamyl, R^2 is hydroxy, lower alkoxy, arloxy, benzyloxy or an alkyl or aryl carbamyl group but is preferably hydroxy and R^3 is typically hydrogen, methyl, ethyl, cyclopropyl methyl or benzyl.

Such compounds include, for example, O-demethyl lycoramine; N-demethyl, O-demethyl lycoramine; N-demethyl N-ethyl lycoramine; N-demethyl N-cyclopropylmethyl lycoramine; N-demethyl N-benzyl lycoramine; O-demethyl lycoramine ethyl ether; deoxy O-demethyl lycoramine; O-deoxy demethyl lycoramine, benzyl ether and dimethyl and phenyl carbamyl analogs of such compounds.

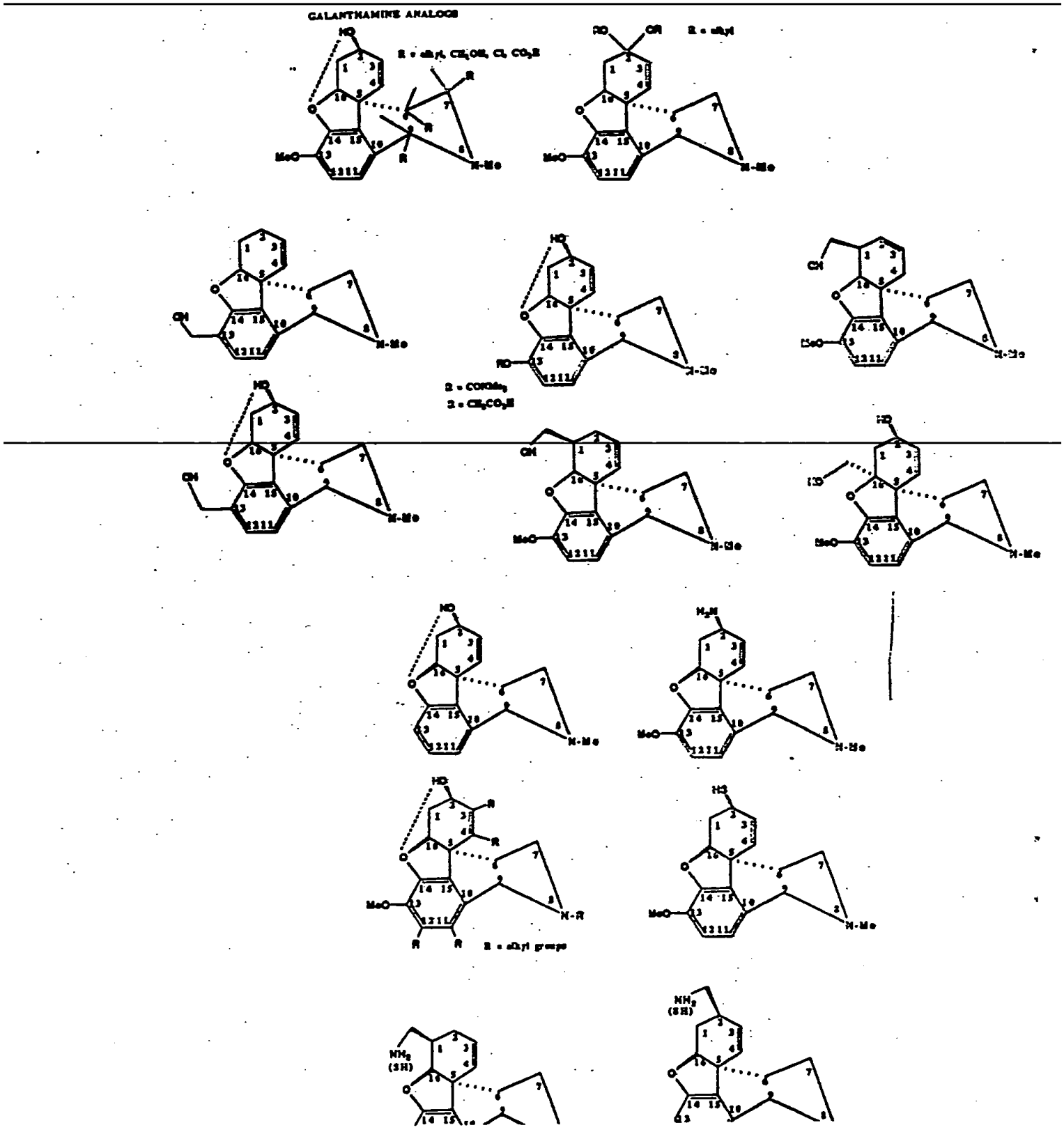
A further class comprising compounds of the formula:



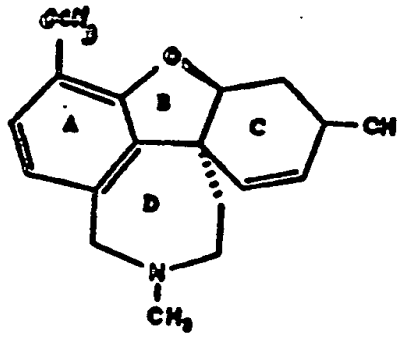
wherein R^3 is selected from hydrogen, lower alkyl, cycloalkyl methyl or benzyl.

Compounds of the above formula I where R_2 is hydroxyl and R_9 is a moiety of formula I wherein R_9 is hydrogen and R_2 is a linking bond are compounds in which the structure of formula I has linked at ring position 2 a hydroxyl group and a second formula I structure wherein R_2 is a bond linking the second formula I structure to said position 2 of the first and in said second formula I structure, R_9 is hydrogen. Such compounds may be made by reacting a compound of formula I wherein R_2 is hydroxyl to convert the hydroxyl to a halide, reacting the halide to form a Grignard compound, and reacting the latter with a galanthamine ketone.

Useful compounds may include the following:



Many compounds of the present invention may be obtained by effecting suitable conversions of galanthamine. Galanthamine has the structure:



Compounds wherein R_1 is other than methoxy can be obtained from galanthamine by demethylation to the corresponding phenol and, if desired, effecting subsequent conversion thereon. Demethylation may be effected with iodotrimethylsilane in accordance with the method described by M.E. Jung and M.A. Lyster in J. Org. Chem. 42 3761 (1977). Reaction with iodotrimethylsilane may be effected in any convenient solvent, for example, chloroform at moderate temperatures (typically 25-40°C) for several hours (e.g. 12-20 hours) to cleave the methyl group.

The phenol obtained by this reaction may be employed itself or used as an intermediate for the production of other active compounds. If it is desired to avoid effecting the same reactions at the allylic hydroxy group in the C ring as are to take place at the phenol group that is produced by demethylation of the A ring when carrying out further interconversions, it is desirable to protect the allylic hydroxyl group. Suitable protection can be effected by converting the allylic hydroxyl group to its tetrahydropyranyl ether or 4-methoxytetra-hydropyranyl ether. Such ethers can be formed by reaction with dihydropyran or 4-methoxytetrahydropyran in a solvent such as dichloromethane at

room temperature in the presence of a strong organic acid such as p-toluenesulfonic acid. When desired, the protection groups can be removed, the tetrahyropyranyl group, for example, by treatment with methanol and Dowex-50 WX8 and the 4-methoxytetrahydropyranyl group by reaction with very dilute (e.g., 0.01N) hydrochloric acid.

The phenolic group obtained by demethylation of the methoxy group of galanthamine may readily be converted into an alkali metal salt by reaction with sodium or potassium hydroxide or reaction with sodium hydride in tetrahydrofuran. The salt so obtained may be "alkylated" by reaction with an appropriate alkyl, aryl, alkaryl or R_5-substituted aryl or alkaryl or heterocyclyl or R_5-substituted heterocyclyl halide to produce a compound wherein R_1 is alkoxy (other than methoxy), aryloxy, alkaryloxy, R_5-substituted aryloxy, R_5-substituted alkoxy or heterocyclyl or R_5-substituted heterocyclyl. The reaction with the halide is typically run with excess halide in the absence of solvent or in a solvent such as dimethyl formamide or dimethylsulfoxide. For less reactive halides, the presence of a silver oxide catalyst may be desirable.

Reaction of the phenolic group with an isocyanate can be used to introduce a monoalkyl or monoaryl carbamyl group.

Dialkyl or diaryl carbamates may be obtained [by] from the mono alkyl or aryl carbamates by reaction with sodium hydride and an alkyl or aryl iodide. For example, the dimethyl carbamate can be obtained by reaction of the hydroxy group with methyl isocyanate followed by reaction with sodium hydride and methyl iodide.

Conversion of the phenolic group to an amino group, which can subsequently be alkylated by conventional means to produce a secondary amine if desired, can be effected by the Bucherer reaction using sodium bisulfite and ammonia.

The phen l group may be esterified, for example, with an acid anhydride or acid halide t produce an

alkanoyloxy or aralkanoyloxy, R_1 group.

Production of compounds wherein R_1 is sulfhydryl or an alkyl-, aryl-, aralkyl-thio group can be effected by first converting the phenolic hydroxyl group obtained by demethylation of galanthamine to a thiol group. This can be effected, for example, by the Newman-Kwart rearrangement described, for example, in S. Patai ed "The Chemistry of the Thiol Group" Part 1 John Wiley & Sons, New York 1974 pages 201-206. This rearrangement is effected in three steps:

(1) conversion of the hydroxyl group to the O-aryl dialkylthiocarbamate by treatment with dialkylthiocarbonyl chloride;

(2) pyrolysis of the O-aryl dialkylthiocarbamate t the S-aryl dialkylthiocarbamate; and

(3) hydrolysis of this product to the aryl mercaptan.

The first stage reaction with dimethylthiocarbamyl chloride may be effected by dissolving the phenol obtained by demethylation of galanthamine in aqueous potassium hydroxide at 10°C or below and then reacting this with dimethyl-thiocarbamyl chloride in tetrahydrofuran at temperatures not exceeding 12°C. The solution is made alkaline and the O-aryl dimethylthiocarbamate is separated. This compound is pyrolyzed at 270-275°C for about 45 minutes in a salt bath, and treated with potassium hydroxide in ethylene glycol. The reaction is cooled, the product extracted and worked up.

The thiol group can be converted to an alkali metal salt if desired by reaction with sodium or potassium hydroxide or sodium hydride. This salt may be alkylated to produce compounds wherein R_1 is alkylthio, arylthio, aralkylthio or alkarylthio by any one of a wide variety of alkylating agents, for example, as described by P.D. Boyer in J. Amer. Chem. Soc. 76 4331 (1954).

The production of the thiol group also provides a convenient route for the production of compounds wherein R_1 is hydrogen. The thiol may be desulfurized, for example, by

refluxing with Raney nickel in absolute alcohol or dioxane, for example, as described by R.L. Augustine "Catalytic Hydrogenation" Marcel Dekker Inc., New York 1965 pp 131-133.

Production of a galanthamine analogue where R_2 is an alkanoyloxy or benzoyl group can be obtained by a simple esterification reaction. Compounds wherein R_2 is alkyloxy, aryloxy, aralkyloxy or alkaryloxy may be formed by forming a salt of the alcohol by reaction with sodium and thereafter reacting the salt with alkyl or other halide as described above for alkylating a phenol salt to produce R_1 as other than methyl.

Similarly, reaction of the hydroxy group with an aryl or alkyl isocyanate will produce compounds wherein R_2 is a monoaryl or monoalkyl carbamate

In other transformations of the R_2 group, the first step in modification will normally be conversion of the allylic alcohol into an allylic bromide. This may be effected by reaction with a slight excess of carbon tetrachloride and triphenylphosphine in a solvent such as methylene chloride at reduced temperature, for example, around 0°C. The bromide may then be reacted with magnesium in a Grignard reaction and the Grignard reagent obtained reacted with water to produce a compound wherein R_2 is hydrogen. Alternatively, reaction of the allylic bromide with lithium aluminum hydride may achieve the same product.

The allyl bromide may also be used as an intermediate for the introduction of other groups into the C ring. For example, the bromide will react with nucleophiles such as sodium or potassium hydrosulfide to replace the bromo group by a hydrosulfuryl group or with sodium cyanide to introduce a cyano group. The hydrosulfuryl group may be converted into a salt and alkylated in the same ways as can a hydrosulfuryl group in the A ring.

The allylic hydroxyl group may also be converted int a keto group. This can be accomplished, for example, by reaction with Jones reagent (H_2CrO_4, H_2SO_4 water and acetone).

Proceeding via the ket group may als be an alternative route to production of compounds wherein R_2 is hydrogen. For example, the keto compound may be reacted with ethane dithiol and boron triflueride etherate and the 1,3-dithiolane produced then desulfurized by reaction with Raney nickel.

The ketone intermediate may also be used as a source for compounds wherein R_2 is amino, such compounds being obtained by reductive amination of the keto group with ammonia and hydrogen in the presence of a nickel catalyst.

Further analogues that can be obtained by use of the ketone as an intermediate are those wherein R_9 is other than hydrogen. These can be obtained by reaction of the ketone with a Grignard reagent.

The ketone may also be used as an intermediate for the production of compounds wherein R_7 is hydroxy methyl by first effecting an α-bromination of the ketone and then converting this to hydroxy methyl.

When R_2 and R_9 jointly form a semi carbazone this can be formed from the ketone by reaction with semi carbazide.

In order to produce compounds wherein R_3 is other than methyl, galanthamine is first demethylated to produce a compound wherein R_3 is hydrogen. Demethylation may be effected by reaction with a chloroformate such as methyl chloroformate or phenyl chloroformate to produce a carbamate which may then be cleaved with hydrazine, or by reaction with ß,ß,ß-trichloromethyl chloroformate followed by reaction with zinc and acetic acid. The resulting amine may then be alkylated with other alkyl groups, branched or unbranched, alkylphenyl group or alkylheterocyclic groups. This reaction may be carried out by converting -NH to the corresponding sodium or potassium salt (NaH, KH) and treating the salt with the corresponding halide, preferably iodides, but bromides and chlorides might be used. All the halides used are commercially available. The reaction conditions may be modified for less reactive halides such as chlorides or aryl or heterocyclic halides which may also be less reactive. For

instance, a special method is needed for N-phenylation as described by D.H.R. Barton, J.P. Finet and J. Khamsi, Tetrahedron Letters 28, 887 (1987).

It is also possible to change the degree of saturation of the "core" structure of galanthamine. For example, if one forms an allylic bromide in the C-ring as described above, this bromide may be subject to catalytic hydrogenation in the presence of palladium, for example, palladium on carbon in ethanol at room temperature and atmospheric pressure to remove not only the bromine atom, but also to saturate the unsaturated bond in the C ring.

The C-ring may be oxidized to produce a further unsaturated bond by oxidation, for example, by heating with nickel, platinum or palladium at 300-350°C or possibly under milder conditions if acceptors such as maleic acid, cyclohexane or benzene are present.

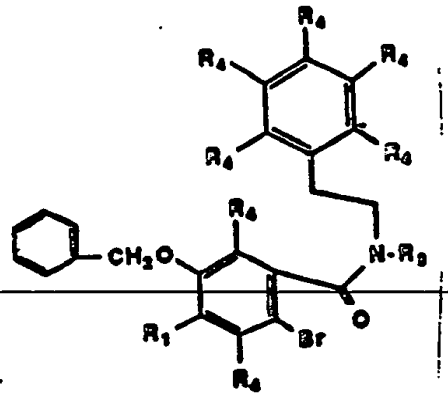
The oxygen of the B ring of galanthamine may be replaced by N-R' by reaction with ammonia or an amine in the gas phase at high temperatures in the presence of activated aluminum oxide or aluminum silicate as described, for example, in Yu. K. Yur'ev and E.G. Vendel'shtein, Zh. Obshch. Khim., 21, 259 (1951); C.A. 45, 7564, (1951); Ibid. 23, 2053 (1953); C.A. 49, 3120 (1955); H. Sugisawa and K. Aso, Tohoku J. Agr. Res., 10, 137 (1959); C.A. 54, 11015 (1960).

R_6 substituents may be introduced into the D-ring for example by Procedure No. 4 hereinafter.

Conversion of R_8 to hydroxy methyl may be effected by photolyzing in the presence of cyanogen chloride to introduce a cyano group. This may be reduced using a Ranez nickel catalyst to produce an aldehyde group that can itself be reduced to hydroxy methyl.

Similar conversions can be effected using lycoramine as starting material to produce compounds wherein the C ring is saturated.

In addition to modifying galanthamine, compounds according to the present invention may also be produced by cyclizing an amide of the formula:



R_1, R_3 and R_4 groups may be selected as desired in the starting material employed. Cyclization is effected by electrochemical oxidation of the type described in U.S. Patent 4,290,862 for preparing narwedine-type enones. The linear precursor in an appropriate solvent with a conductive salt and 2% HBF_4 or $KClO_4$ or K_2CO_3 is added to the anode compartment of an electrolytic cell. The cathode compartment and the electrolytic bridge of the reference electrode contains the same anodic solvent and the same percentage of conductive salt. The working electrode is platinum. Oxidation is carried out at 1.3 volts at low temperatures (below 0^oC). This procedures after workup of the product affords cyclization products.

The compounds of the present invention may be used for the treatment of Alzheimer's disease either in free base form or as the acid addition salts.

The compounds can be administered in any convenient chemical or physical form. For example, they may be administered as pharmaceutically acceptable salts, as long as these do not quaternise the D-ring nitrogen atom. Useful salts include the hydrobromide and hydrochloride.

The compounds or the pharmaceutically-acceptance acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous or injection. Sustained release delivery mechanisms are particularly useful for administration of the compounds of the present invention, for example, intracerebroventricularly by means of an implanted reservoir by use of sustained release capsules or by means of a trans dermal patch. It may be necessary to begin at lower doses than are ultimately effective.

Certain of the compounds may be only sparingly soluble in water at room temperature and so injectable compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1-50 mg/ml more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, typically 20-30 mg/ml of the compound of the present invention. Typical dosage rates when administering compounds of the invention will depend upon the exact nature and condition of the patient. For example, typical dosage rates for administration by injection are in the range 5-1,000 mg per day depending upon the patient. In some cases, even lower dosages such as 0.5 or 1 mg per day may be helpful. For example, divided doses in the range 0.5-5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50-300 mg per day to a patient of a body weight of 40-100 kg, although in appropriate cases such dosages may

prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

The compounds of the invention may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100-600 mg per day. In preparing such tablets or capsules, standard tablet or capsule-making techniques may be employed. The dosage rate of the compound of the invention or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing tablets. Capsules may be prepared using soft gelatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of active compound which release the contents over a period of several hours thereby maintaining a constant level of active compound in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacy in Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological

alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945-952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg hydrobromide of a compound according to the invention to be taken four times a day, or a sustained-release-preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5mg/5ml and 25mg/5ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. If such problems occur with the compounds of the present invention, it may be desirable to administer compounds of the invention in conjunction with another drug such as propanthelinbromide to control such arrythmias. As with other drugs that act on the central nervous system, minor side effects, such as nausea, may be noted. In this case, the compounds of the present invention will be administered in conjunction with agent for control of such side effects.

A substantial proportion of patients suffering from Alzheimer's disease exhibit not only reduced levels of acetyl choline but also of norepinephrine in the brain. In such cases, the compounds of the present invention may advantageously be employed in conjunction with compounds such as clonidine desipramine, monoamine oxidase inhibitors, methamphetamine and methyl phenidate that stimulate the noradrenergic receptors in the brain.

PROCEDURES:

1. Conversion of oxygen to nitrogen in furanoid ring.

This transformation has been accomplished by several authors. Passage of furan and its homologs, or reduced furans with ammonia over alumina, at 400-450°C, affords the corresponding pyrroles. With primary, amines the N-substituted pyrrole is obtained. A typical procedure is as follows. The furan derivative is dissolved in liquid ammonia and passed over an alumina catalyst (200 c.c. 4-6 mesh) which has been preheated to 400°C.[1] Alternatively, a mixture of a furan derivative and ammonia in aqueous-alcoholic medium may be heated at temperature around 110°-150°C. The reaction proceeds more readily under pressure and therefore can be carried out in an autoclave.[2]

1. C.L. Wilson, *J. Chem. Soc.* 63. 1945.
2. R.C. Fuson, C.L. Fleming, R. Johnson, *J. Am. Chem. Soc.* 60, 1994 (1938).

2. Introduction of -CH_2OH at position 16.

Position 16 is next to the furan ring. This position is equivalent to the α-position of an ether and therefore prone to radical attack by reagents such as oxygen, peroxides, and photochemical reactions.

Irradiation of cyclic ethers in the presence of cyanogen chloride is known to produce α-cyano ethers in good yields.[1] Therefore, a similar reaction on galanthamine should introduce a cyano group in this position. The cyano group is known to be converted to an aldehyde with Raney Nickel and formic acid.[2] The aldehyde may in turn be reduced with any reducing agents to the hydroxymethyl group.[3]

A typical procedure is as follows. The photolysis is carried out using a mercury lamp S-81 in a water cooled, unfiltered quartz immersion well. A solution of equimolar amounts of galanthamine and cyanogen chloride, in a spectral grade solvent, is irradiated with stirring, in a nitrogen atmosphere, and in a quartz cell. The reaction is irradiated for 2h in the presence of sodium bicarbonate. The sodium bicarbonate is essential to absorb the hydrogen chloride. Lower yields are obtained in the absence of the reagent.

The final mixture is filtered, concentrated, washed with appropriate reagents and dried. Removal of solvent affords the product.

The cyano derivative obtained is dissolved in 75% (v/v) of aqueous formic acid and treated with a 50:50 Ni-Al alloy (Raney type). The mixture is heated for 3h at 95°C, diluted with absolute ethanol-ethyl acetate and filtered through Celite. The filtrate is concentrated, washed with appropriated reagents and dried. Removal of solvent affords the product.

The aldehyde derivative is dissolved in isopropanol and added to a solution of sodium hydroxide and sodium borohydride, dropwise, at such rate that the reaction refluxes gently. After standing overnight, the reaction is worked up as usual.

1. E. Muller, H. Huber, *Chem. Ber.* **96**, 2319 (1963).
2. T. van Es, B. Stakun, *J. Chem. Soc.* 5775 (1965).
3. S.R. Sandler, W. Karo, *Organic Functional Group Preparations"*, **Vol 12,** 1968. Academic Press, pp. 89-90.

3. Conversion of -OMe at position 13 to other substituents.

The reaction will require demethylation of the methoxy group. Although demethylation of aromatic alkoxy group is considered a standard reaction, this operation may be tricky in polysubstituted systems. A successful approach is the reaction of boron tribromide at 0°C.[1] The phenol obtained may be converted to a bromide by standard procedure.[2] Generation of a lithium anion at this position[3] allows a variety of reactions such as treatment with alkyl halides to give alkyl groups, carbon dioxide to afford acids or aldehydes and ketones to give alcohols.

A typical procedure follows. A 1M solution of boron tribromide is added dropwise to a solution of galanthamine in dry methylene chloride at 0°C, under nitrogen. After stirring at 0°C for 3h, the excess reagent and boron complexes are hydrolyzed by water. The product is obtained by extraction of the aqueous layer with ether. Removal of the solvent affords the compound.

The phenol derivative is mixed thoroughly with phosphorus pentabromide and heated at 70-80°C, then at 120°C. Hydrolysis with ice and water affords the crude bromo compound which may be recrystallized from an appropriate solvent.

A solution of n-butyl lithium was added dropwise, at -78°C, under argon, to the bromo derivative dissolved in tetrahydrofuran and hexamethyl phosphoramide to generate the intermediate anion.

To this anion, one may add any alkyl halide to form an derivative. Alternatively, the solution could be poured over dry ice to afford the corresponding carboxylic acid, or to an aldehyde or ketone to form the corresponding alcohol derivative. Treatment of this anion with ethyl chloracetate would give the corresponding ethyl carboxymethyl derivative. The above methodology is general to introduce various groups in place of the methoxy group in the aromatic ring (position 13).

1. S-Y Han, J.T. Gordon, K. Bhat, M.B. Dratman, M.M. Joullie', *Int. J. Peptide Protein Res.* 30, 1987, 652.

2. C.E. Kaslow and M.M. Marsh, *J. Org. Chem.* 12, 456 (1947).

3. J. Chiarello and M.M. Joullie', *Tetrahedron,* 44, 41 (1988).

4. Conversions in the D ring

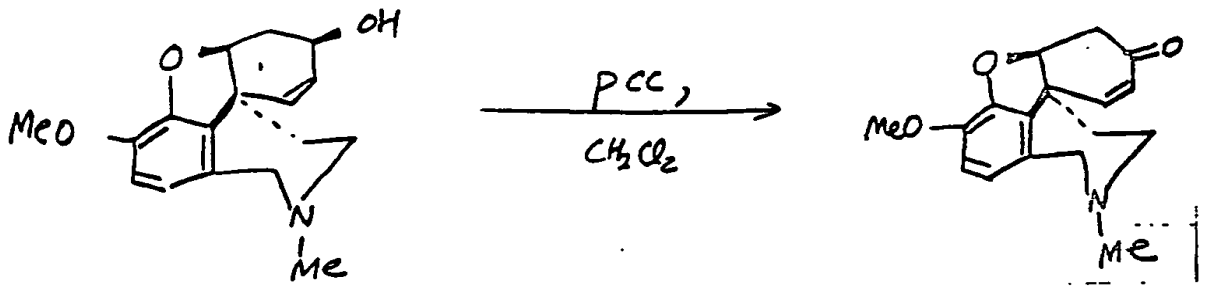
Removal of the methyl group in the D ring of galanthamine can be accomplished by the classical von Braun reaction.1 The reaction may be manipulated to give either demethylation to a secondary amine or to open the ring. Either of these procedures will give rise to new analogs. Ring opening would afford two chains, one at position 10, possibly a bromoethyl groups and one at position 5, a N-methyl propylamine. These could be used to study the effect of disrupting ring D.

However, demethylation would serve to introduce functionality in ring D *via* the formation of an imine. A typical procedure for introduction of substituents in ring D follows. Treatment of N-demethylated galanthamine with tert-butyl hypochlorite at 0oC will afford the N-chloro derivative. This sensitive compound is not isolated but immediately dehalogenated with either sodium methoxide or diazabicycloundecene to afford the highly unstable pyrroline. This intermediate can be treated with nucleophiles3 or with benzoic and, *tert*-butylisonitrile as described in reference 2.

1. H.A. Hagerman, *Org. Reactions*, VII, Chap 4 (1953).
2. R.F. Nutt, M.M. Joullie', *J. Am. Chem. Soc.*, 104, 5852 (1982).
3. J. Hausler, U. Schmidt, *Liebigs Ann. Chem.* 1881 (1979).

The production of compounds f the present invention is illustrated by the following Examples:

EXAMPLE 1

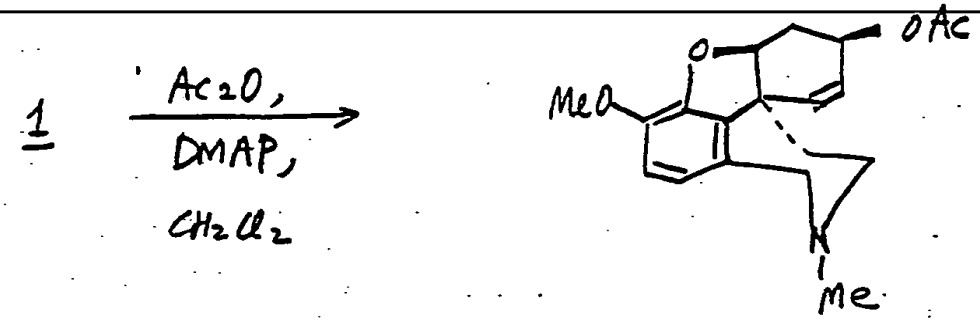


1

To a solution of Galanthamine (1, 0.7g, 0.2439 mmoles) in dry methylene chloride (4 ml), pyridinium chlorochromate (0.1577g, 0.7317 mmoles) was added and stirred at room temperature for 8 hours. The reaction mixture was diluted with methanol and filtered. Removal of solvent followed by purification on a silica gel column using acetone, methanol:acetone (10:90) as eluants afforded the desired product. (0.06g, 86% yield).

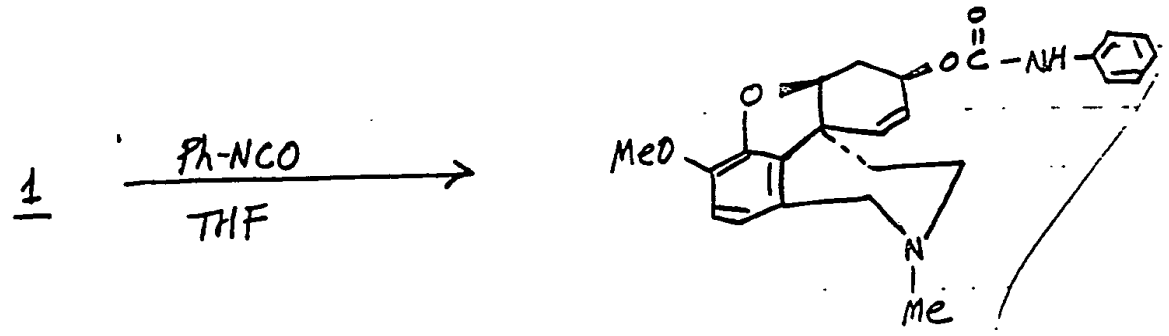
mp. 184-186°C

EXAMPLE 2



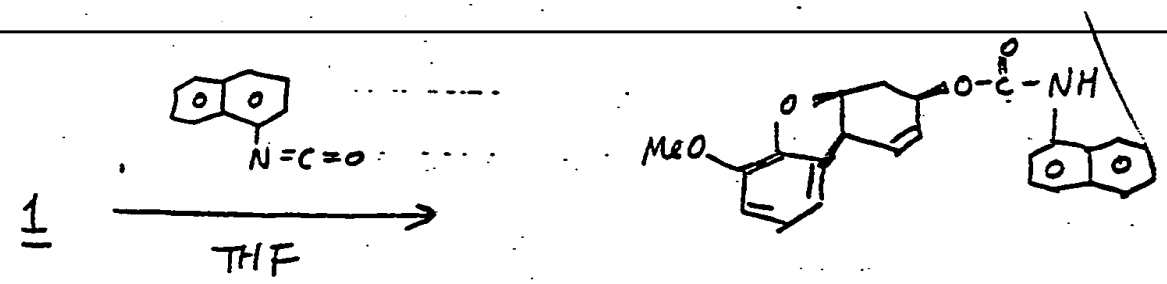
To a solution of 1 (0.07g, 0.2439 mmoles) in methylene chloride, acetic anhydride (0.03 ml, 0.317 mmoles) and dimethylaminopyridine (0.0536g, 0.439 mmoles) were added at 0°C in an ice bath. The reaction mixture was stirred at)°C for 10 minutes and room temperature for 60 minutes. Solvents were removed on a rotary evaporator and the residue was diluted with ethyl acetate, washed with water, 10% Na_2CO_3, brine and dried (Na_2SO_4) concentration of the solvent and purification by silica gel chromatography using Acetone, MeOH:Acetone (1:10) as eluants afforded 0.0773g of product (96% yield).
mp. 126-128°C

EXAMPLE 3



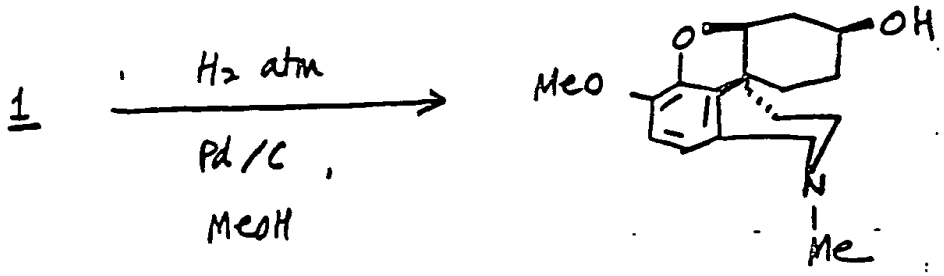
Phenylisocyante (0.033 ml, 0.2926 mmoles) was added to a stirred solution of 1 (0.07 g, 0.2439 mmoles) in the THF (5 ml) at room temperature, and then stirred for 30 hours at the same condition. The reaction mixture was concentrated, purified by silica gel column chromatography using Acetone, MeOH:Acetone (10:90) to give 0.0982g (99% yield) of product. mp 79-81°C

EXAMPLE 4



1-Naphthyl isocyante (0.042 ml, 0.2926 mmoles) was added to a stirred solution of 1 (0.07g, 0.2439 mmoles) in THF (5 ml) at room temperature. The reaction mixture was stirred for 24 hours at room temperature, and then concentrated. The crude reaction mixture was purified by silica gel column chromatography using acetone, methanol:acetone (10:90) as eluants to afford 0.11g of product (99%).
mp. 198-200°C

EXAMPLE 5



To a solution of 1 (0.1g, 0.3484 mmoles) in methanol, 20% palladium on carbon (0.02g) was added and hydrogen atmosphere was applied. The reaction mixture was stirred for 10 hours at room temperature. The catalyst was filtered off through celite, washed thoroughly with methanol. The solution was concentrated, and the crude material was purified on a silica gel column using acetone:methanol (90:10, 80:20) to afford 0.0938g (93% yield) of the product.
mp 110-112°C

Anticholinesterase activity of the compounds of the above examples was assayed by an assay for inhibition of acetylcholinesterase following the procedure of G. Ellman, Biological Pharmacology, 1961, Vol. 7, pp 88-95. Acetylthiocholine serves as substrate since it acts like acetylcholine. Acetylcholinesterase cleaves it to thiocholine and acetate which react with dithiobisnitrobenzoate to form a yellow color which is measured photometrically.

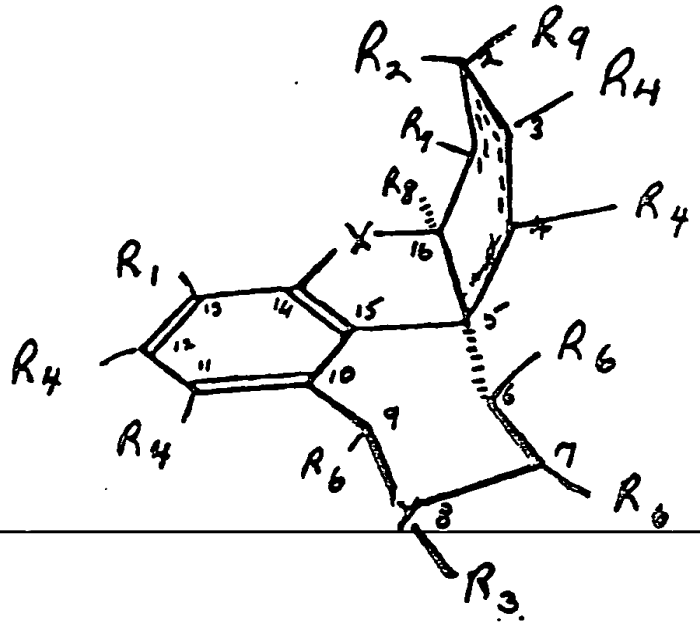
The assay results are shown in the following table, which also includes an assay of the activity of galanthamine.

TABLE

COMPOUND	PERCENT INHIBITION OF ACETYLCHOLINESTERASE
Galanthamine	95%
Product of Example 1	10%
Product of Example 2	37%
Product of Example 3	37%
Product of Example 4	60%
Product of Example 5	30%

C L A I M S

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of a compound of the formula I



wherein the broken line represents an optionally present double bond in one or the two of the portions shown, R_1 and R_2 are each selected independently from the group consisting of hydrogen, hydroxyl, amino or alkylamino, cyano, sulfhydryl, alkoxy of 1-6 carbon atoms, alkylthio, aryloxy, arylthio, R_5-substituted aryloxy, R_5-substituted arylthio, aralkoxy, an aliphatic or aryl carbamyl group wherein the aliphatic or aryl moiety may be R_5 substituted or unsubstituted, aralkylthio, R_5-substituted aralkoxy, R_5-substituted aralkylthio, aryloxymethyl, R_5-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_5-substituted benzoyloxy, aryloxy carbonyl and R_5-substituted aryloxy carbonyl, R_1 may als by alkyl of up to 14 carbon atoms, or hydroxy methyl, R_2 may also be carboxymethyl provided that at

least one of R_1 and R_2 is hydroxy, amino or alkylamino unless R_7 or R_8 is hydroxymethyl,

R_3 is hydrogen, straight or branched chain alkyl, of 1-6 carbon atoms, cycloalkyl methyl, phenyl, R_5 substituted phenyl, alkylphenyl, R_5-substituted alkylphenyl, heterocyclyl selected from α- or ß-furyl, α or ß-thienyl or thenyl, pyridyl, pyrazinyl and pyrimidyl, alkyl heterocyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy

each R_4 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thioaryloxy, alkarloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo iodo and trifluoromethyl,

R_5 is selected from the same groups as R_4,

R_6 is hydrogen, halo, trifluoromethyl or alkyl of 1 to 4 carbon atoms,

R_7 is selected from the same groups as R_4 or may be hydroxy alkyl of 1-2 carbon atoms,

R_8 is hydrogen or hydroxymethyl,

R_9 is hydrogen or alkyl of 1 to 6 carbon atoms, or when R_2 is hydroxyl R_9 may be a moiety of formula I wherein R_9 is hydrogen and R_2 is a linking bond; or

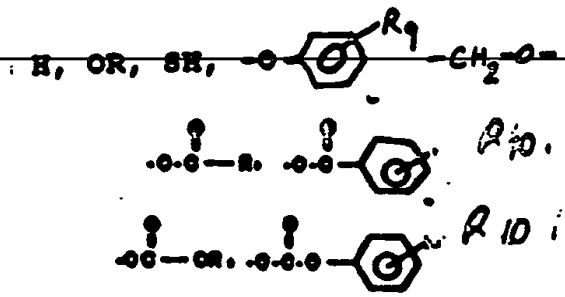
R_2 and R_9 may jointly form a semi carbazone,

X is oxygen or NR_5,

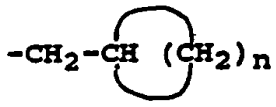
Y is nitrogen or phosphorus

and methylenedioxy derivatives thereof with the proviso that when X is O, R_3 is not methyl when R_1 is methoxy, R_2 is hydroxy, and all R_4 are hydrogen or a pharmaceutically-acceptable acid addition salt thereof.

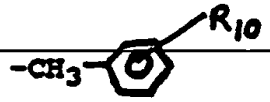
2. A method according t claim 1 wherein the compounds used is one wherein R_1 and R_2 are each selected from



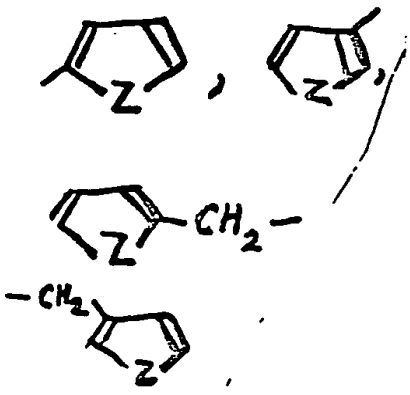
wherein R is alkyl 1-6 carbon atoms or phenyl or R^5-substituted phenyl or benzyl or R^5-substituted benzyl, wherein R_{10} is hydrogen, alkyl or alkoxy, R_3 is -H, or branched on linear alkyl or



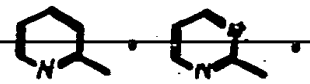
wherein n is 3, 4 or 5



wherein R_{10} is as defined above

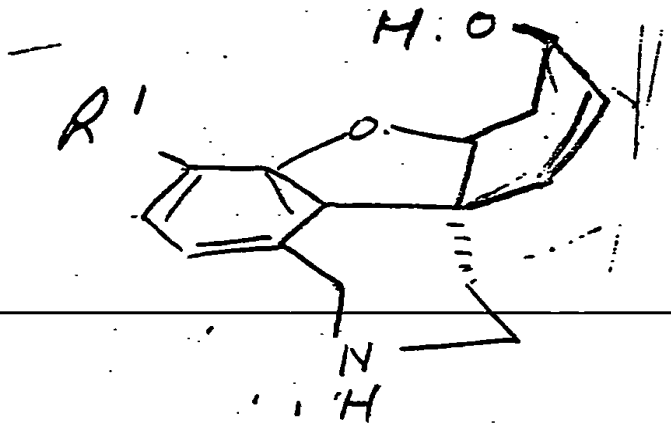


where Z is O, S, or NH

or 

X is oxygen and Y is nitrogen.

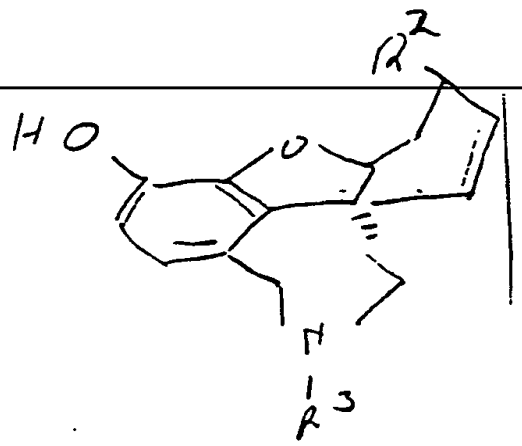
3. A method according to claim 1 wherein said compound is of the formula:



wherein R^1 is as defined in claim 1, preferably hydroxy, lower alkoxy, aryloxy, R^5 substituent aryloxy, benzyloxy or R^5 substituted benzyloxy, amino, alkyl amino or an alkyl or aryl carbamyl group.

4. A method according to claim 3, wherein said compound is selected from O-demethyl, N-demethyl galanthamine; O-ethyl, O-demethyl, N-demethyl galanthamine; O-phenyl, O-demethyl, N-demethyl galanthamine; and O-benzyl, O-demethyl galanthamine.

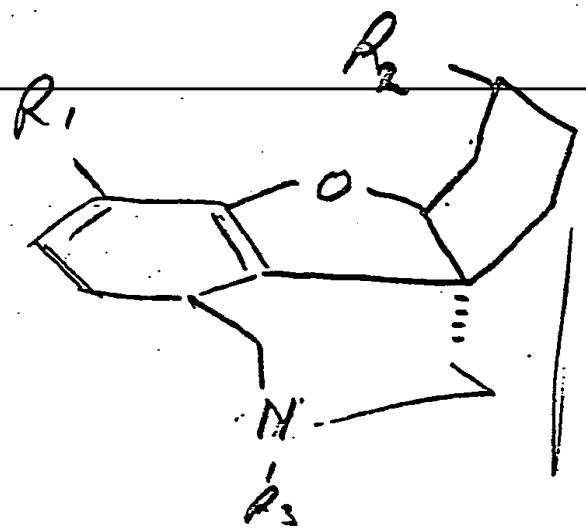
5. A method according to claim 1 wherein said compound is of the formula:



wherein R^2 is hydroxy, lower alkoxy, arloxy, R^5 substituted arloxy benzyloxy or R^5 substituted benzyloxy or an alkyl or aryl carbamyl group and R^3 is hydrogen or alkyl of 1-6 carbon atoms such as methyl or ethyl, methyl cyclopropyl or benzyl or R^5-substituted benzyl.

6. ~~A method according to claim 5, wherein said compound~~ is selected from O-demethyl galanthamine; O-demethyl galanthamine; O-methyl ether; O-demethyl galanthamine; O-ethyl ether; O-demethyl galanthamine, O-benzyl ether; O-demethyl galanthamine, phenyl and O-demethyl N-demethyl galanthamine, -naphthyl carbamates; O-demethyl galanthamine dimethyl carbamate and O-dimethyl galanthamine diethyl carbamate wherein the carbamyl group is bonded to the oxygen of the cyclohexene ring, and the corresponding N-demethyl and N-demethyl N-ethyl and N-demethyl N-cyclopropyl methyl and N-demethyl N-benzyl compounds.

7. A method according to claim 1, wherein said compound is of the formula:

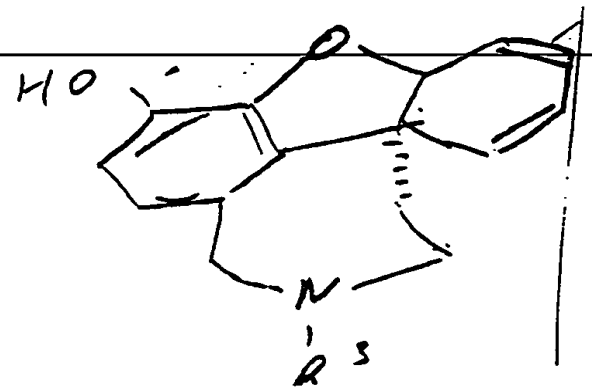


wherein R^1, R^2 and R^3 are as defined in claim 1.

8. A method according to claim 7, wherein the compound employed is one wherein R^1 is typically being hydroxy, lower alkoxy, benzyloxy or R^5 substituted benzyloxy, amino alkylamino or alkyl or aryl carbamyl, R^2 is hydroxy, lower alkoxy, arloxy, benzyloxy or an alkyl or aryl carbamyl group but is preferably hydroxy and R^3 is hydrogen, methyl, ethyl, cyclopropyl methyl or benzyl.

9. A method according to claim 8, wherein said compound is selected from O-demethyl lycoramine; N-demethyl, O-demethyl lycoramine; N-demethyl N- ethyl lycoramine; N-demethyl N-cyclopropylmethyl lycoramine; N-demethyl N-benzyl lycoramine; O-demethyl lycoramine ethyl ether; deoxy O-demethyl lycoramine; O-deoxy demethyl lycoramine, benzyl ether and dimethyl and phenyl carbamyl analogs of such compounds.

10. A method according to claim 1, wherein said compound is of the formula:



wherein R^3 is selected from hydrogen, lower alkyl, cycloalkyl methyl or benzyl.

11. A method according to any one of the preceding claims, wherein the administration is parenteral at a daily dosage of 0.5-1,000 mg of a compound of formula 1 as claimed in claim 1 or a pharmaceutically-acceptable acid addition salt thereof.

12. A method according to any one of the preceding claims, wherein said dosage rate is 50-300 mg per day.

13. A method according to any one of preceding claims 1-10, wherein said administration is oral and is in the range 10-2000 mg per day.

14. A method according to claim 13, wherein said dosage rate of 100-600 mg per day.

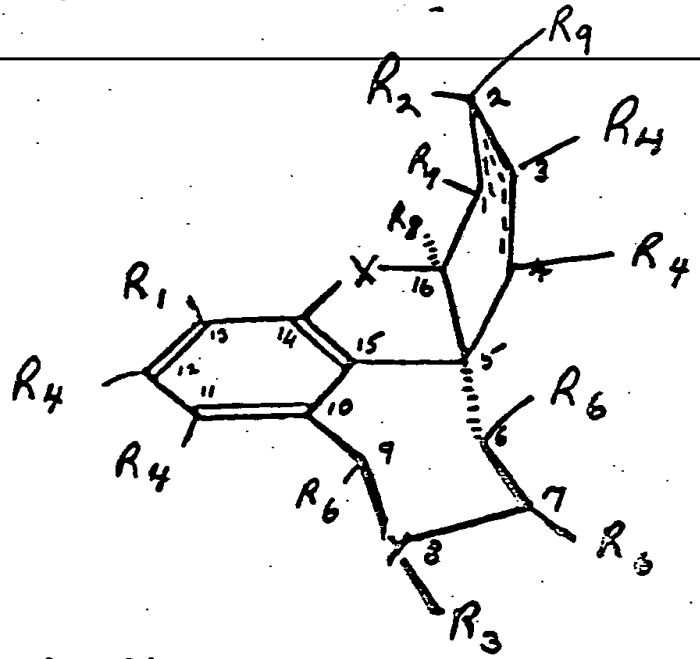
15. A method according to any one of claims 1-10, wherein a compound according to any one of claims 1-10 is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

16. A method according to any one of claims 1-10, wherein a compound according to any one of claims 1-10 is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

17. A method according to any one of claims 1-10,

wherein a compound according to any one of claims 1-10 is administered in a sustained release formulation.

18. A compound of the formula



wherein the broken line represents an optionally present double bond in one of the two portions shown, R_1 and R_2 are each selected independently from the group consisting of hydrogen, hydroxyl, amino or alkylamino, cyano, sulfhydryl, alkoxy preferably of 1-6 carbon atoms, alkylthio, aryloxy, arylthio, R_5-substituted aryloxy, R_5-substituted arylthio, aralkoxy, an aliphatic or aryl carbamyl group wherein the aliphatic or aryl moiety may be R_5 substituted or unsubstituted, aralkylthio, R_5-substituted aralkoxy, R_5-substituted aralkylthio, aryloxymethyl, R_5 substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_5-substituted benzoyloxy, aryloxy carbonyl and R_5-substituted aryloxy carbonyl, R_1 may also by alkyl of up to 14 carbon atoms, or hydroxy methyl, R_2 may also be keto; R_2 may also be carboxymethyl provided that at least one of R_1 and R_2 is hydroxy amino or alkylamino unless R_7 or R_8 is hydroxymethyl,

R_3 is hydrogen, straight or branched chain alkyl,

preferably of 1-6 carbon at ms, cycloalkyl methyl, alkylphenyl, R_5-substituted alkylphenyl, heterocyclyl such as α- or ß-furyl, α- or ß-thienyl or thenyl, pyridyl, pyrazinyl or pyrimidyl groups, alkyl heterocyclyl and R'-substituted heterocyclyl, where R_1 is alkyl or alkoxy

each R_4 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, aryl, aralkyl, alkoxy, thioalkoxy, aryloxy, thioaryloxy, alkarloxy, thioalkaryloxy, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo iodo and trifluoromethyl, and R_5 is selected from the same groups as R_4,

R_6 is hydrogen, halo, trifluoromethyl or alkyl of 1 to 4 carbon atoms,

R_7 is selected from the same groups as R_4 or may be hydroxy or mercapto alkyl of 1-2 carbon atoms,

R_8 is hydrogen or hydroxymethyl,

R_9 is hydrogen or alkyl of 1 to 6 carbon atoms, or when R_2 is hydroxyl R_9 may be a moiety of formula I wherein R_9 is hydrogen and R_2 is a linking bond; or

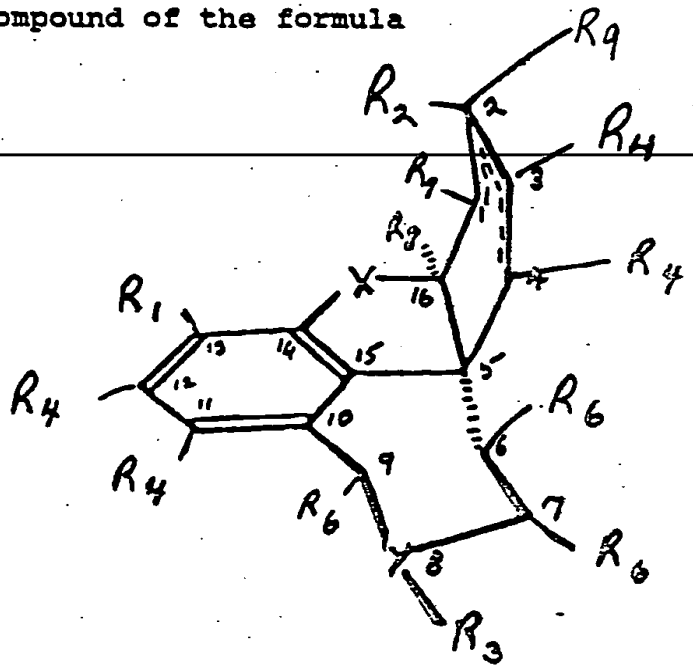
R_2 and R_9 may jointly form a semi carbazone,

X is nitrogen,

Y is nitrogen or phosphorus

and oxidized and reduced and methylenedioxy derivatives thereof with the proviso that when X is O, R_3 is not methyl when R_1 is methoxy, R_2 is hydroxy, and all R_4 are hydrogen and pharmaceutically-acceptable acid addition salts thereof.

19. A compound of the formula



wherein the broken line represents an optionally present double bond in one of the two portions shown, R_1 and R_2 are each selected independently from the group consisting of hydrogen, hydroxyl, amino or alkylamino, cyano, sulfhydryl, alkoxy preferably of 1-6 carbon atoms, alkylthio, aryloxy, arylthio, R_5-substituted aryloxy, R_5-substituted arylthio, aralkoxy, an aliphatic or aryl carbamyl group wherein the aliphatic or aryl moiety may be R_5 substituted or unsubstituted, aralkylthio, R_5-substituted aralkoxy, R_5-substituted aralkylthio, aryloxymethyl, R_5-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_5-substituted benzoyloxy, aryloxy carbonyl and R_5-substituted aryloxy carbonyl, R_1 may also by alkyl of up to 14 carbon atoms, or hydroxy methyl, R_2 may also be keto; R_2 may also be carboxymethyl provided that at least one of R_1 and R_2 is hydroxy amino or alkylamino unless R_7 or R_8 is hydroxymethyl,

R_3 is hydrogen, straight or branched chain alkyl, preferably of 1-6 carbon atoms, cycloalkyl methyl, alkylphenyl, R_5-substituted alkylphenyl, heterocyclyl such as

α- or β-furyl, α- or β-thienyl or thenyl, pyridyl, pyrazinyl or pyrimidyl groups, alkyl heterocyclyl and R'-substituted heterocyclyl, where R_1 is alkyl or alkoxy

each R_4 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, aryl, aralkyl, alkoxy, thioalkoxy, aryloxy, thioaryloxy, alkaryloxy, thioalkaryloxy, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo iodo and trifluoromethyl, and R_5 is selected from the same groups as R_4,

R_6 is hydrogen, halo, trifluoromethyl or alkyl of 1 to 4 carbon atoms,

R_7 is selected from the same groups as R_4 or may be hydroxy or mercapto alkyl of 1-2 carbon atoms,

R_8 is hydrogen or hydroxymethyl,

R_9 is hydrogen or alkyl of 1 to 6 carbon atoms, or when R_2 is hydroxyl R_9 may be a moiety of formula I wherein R_9 is hydrogen and R_2 is a linking bond; or

R_2 and R_9 may jointly form a semi carbazone,

~~X is oxygen,~~

Y is nitrogen or phosphorus

and oxidized and reduced and methylenedioxy derivatives and pharmaceutically-acceptable acid addition salts thereof with the proviso that when X is O, R_3 is not methyl when R_1 is methoxy, R_2 is hydroxy, and all R_4 are hydrogen provided that when the 3-4 bond is saturated, R_1 is not hydrogen when R_2 is methoxy or hydroxy, R_4 is hydrogen, R_3 is methyl and R_7 is hydrogen or ethoxy, and R_1 is not acetoxy when R_2 is hydroxy, R_3 is methyl, R_4 is hydrogen and R_7 is hydrogen and when R_2 is hydroxy, R_3 is not hydrogen or benzyl when R_1 is methoxy and all of R_4 and R_7 are hydrogen, and further provided that the compound is not leucotamine, O-methyl leucotamine, O-methyl leucotamine acetate, sanguinine, lycoramine, O-demethyl lycoramine, childanthine, habranthine, N-formyl galanthamine, acetyl dihydrogalanthamine or N,O-diacetyl N-demethylgalanthamine, deoxydemethyl lycoramine, lycoramine acetate, deoxylycoramine or deoxydemethyl

lycoramine carbamate.

20. A medicine for treatment of Alzheimer's disease and related dementias comprising a compound as specified in claim 1.

21. A medicine according to claim 20 in the form of a sustained release product.

22. Use of a compound as specified in claim 1 for the production of a pharmaceutically composition for treatment of Alzheimer's disease or related dementias.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/01542

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 31/55 C07D 491/06, C07D 487/06
U.S.Cl.: 514/215; 540/581, 540/577

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC(4):	A61K 31/55
U.S.Cl.:	514/215; 540/581; 540/577

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

C.A.S. ONLINE

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	A.G. Schultz, J. Amer. Chem. Soc. 99, 8065 (1977). See 9a on page 8066.	19
A	Chemical Abstracts, Volume 73, No 4. issued 27 July 1970 (Columbus, Ohio, USA) J.G. Bhandarkar, "Structure and Biosynthesis of Chlidanthine". See page 392, column 1, Abstract No. 25709h, J. Chem. Soc. C 1970 (9), 1224-7. See (I)	19
X	Chemical Abstracts, Vol. 51, No. 11 issued 10 June 1956 (Columbus, Ohio, USA) H.G. Boit, "Amaryllidacae Alkaloids". The Abstract at 8120f, Chem. Ber. 89, 2462-5 (1956).	19
A	Chemical Absracts, Vol. 85. No. 21 issued 22 November 1976 (Columbus, Ohio USA) S. Kobayashi, "Alkaloids of the Amaryllidaceae". See page 577, Col. 1, Abstract No. 160383k, Chem. Pharm. Bull. 1976, 24(7) 1537-43.	19

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

04 OCTOBER 1988

Date of Mailing of this International Search Report

18 OCT 1988

International Searching Authority

ISA/US

Signature of Authorized Officer

MARK L. BERCH

Form PCT/ISA/210 (second sheet) (Rev.11-87)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y,P	US, A, 4,663,318 (DAVIS) 5 May 1987. See Abstract.	1-20

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	Chemical Abstracts, Vol. 95. No. 3 issued 20 July 1981 (Columbus, Ohio, USA) S. Kobayashi, "Isolation of O-demethyl coramine from bulbs of Lycoris Radiata Herb". See page 728 column 1, Abstract No. 25351q Chem. Pharm. Bull. 1980, 28(11) 3433-6.	19
A	Chemical Abstracts, Vol. 103, No. 1 issued 8 July 1957 (Columbus, Ohio, USA), Losev, "Treatment of Parkinsonianism with metamisyl". See page 61, col. 2, the Abstract No. 625c Otkrytiya, Izobret. 1985 (13),12.	19

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [2] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [3], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

I. Compounds and use for X=O, Y=N 1(part), 2-10, 11-17(part), 19-22(part).
II. Compounds and use for X=N, Y=P 1(part), 11-18(part), 20-22(part).
III. Compounds and use for X=O, Y=P 1(part), 11-17(part), 19-22(part).

See Attachment sheet 1.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims: 1(part) 2-10, 11-18(part), 19-22(part)

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4 ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING (CONTINUED)

IV. Compounds and use for X=N, Y=N 1(part), 11-18(part), 20-22(part)

These lack unity under PCT Rule 13 because they are structurally distinct. Each Group defines a different heterocycle. These 4 heterocyclic ring systems are not equivalent, nor could they be considered as such.